10 mg/kg で 16.1%から 23.4%であった。

マウス，ラット及びサル（いずれも雌雄）にレンボレキサントを反復経口投与したとき，マウス及びラットの暴露量に性差が認められたが，サルの雌雄の暴露量は同等であった。反復投与による暴露量の蓄積が観察された。

雄 SD ラット及び雄カニクイザルにそれぞれ 10 及び 3 mg/kg の[^{14}C]レンボレキサントを単回経口投与した後，[^{14}C]レンボレキサントは速やかに吸収され，投与 0.83 及び 1.8 時間後に最も高い血液中放射能濃度を示した。ラット，サルともに血液中放射能濃度の $t_{1/2}$ は 110 時間であった。いずれの種においても投与した放射能は主に糞中に排泄され，尿中への排泄は比較的少なかった。投与された放射能の大部分は排泄物中に回収され，ラットでは投与後 168 時間までに投与された放射能の 96.5%が，サルで投与後 336 時間までに 97.5%が回収された。雄 SD ラットに[^{14}C]レンボレキサントを経口投与後，放射能は組織内に広く分布した。放射能は投与後 336 時間以内に多くの組織からほぼ完全に消失し，全ての組織で残留放射能は最高放射能濃度の 1%以下若しくは定量限界値未満となった。雄有色ラット(Brown Norway)に 10 mg/kg の[^{14}C]レンボレキサントを単回経口投与したとき，全ての組織で放射能濃度は速やかに消失し，投与後 24 時間までに最高値の 9%以下に低下した。肺及び脾臓を除く全ての組織における放射能濃度は投与後 336 又は 672 時間で定量限界を下回った。肺及び脾臓では投与 672 時間後にも放射能が低濃度で検出され，比較的緩やかに消失し，放射能の $t_{1/2}$ はそれぞれ 1330 時間（55.4 日）及び 2210 時間（92.1 日）であったが，非臨床安全性試験では肺又は脾臓におけるレンボレキサント由来の所見は観察されなかった。また，有色ラットにおけるメラニン含有組織（皮膚及び眼球）への放射能の蓄積は認められなかった。

CD-1 マウス，SD ラット，カニクイザル及びヒトにおけるレンボレキサントの血漿中タンパク結合率はいずれの動物種においても比較的高く，78.4%～88.7%（検討濃度：100～1000 ng/mL）であった。ヒト血漿においてレンボレキサントは，主に HSA，LDL 及び HDL に結合した。CD-1 マウス，SD ラット，カニクイザル及びヒトにおける R_B 値は 0.610 から 0.964（検討濃度：100～1000 ng/mL）であった。マウス，ラット，サル及びヒトにおけるレンボレキサント及びその代謝物（M4，M9 及び M10）の in vitro 血漿タンパク結合率及び R_B 値には濃度依存的な変動は認められなかった（検討濃度：100～1000 ng/mL）。

ラット，サル及びヒトの in vitro 試料及び生体試料の代謝物分析から，全ての動物種においてレンボレキサントの主消失経路は代謝によるものであり，レンボレキサントは，酸化代謝を一次代謝反応とする多様かつ逐次的な経路を介して代謝されることが示された。レンボレキサントは，最初に複数の一酸化体に代謝され，そのいくつかは，さらに酸化されてカルボン酸体又は二酸化体に代謝され，さらに抱合代謝を受けた。なお，ヒトに特異的な血漿中代謝物は認められなかった。

ヒトマスバランス試験（外国 007 試験［E2006-A001-007，5.3.3.1.4］）において，M10 のみが血漿中の薬物関連総暴露量の 10%以上を示す主要な血漿中代謝物であった。そのため，FDA の metabolites in safety testing（MIST）ガイダンス（“Safety Testing of Drug Metabolites. Guidance for Industry” US FDA, 2016）及び International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M3(R2) ガイダンス（“Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”, 2012）の勧

告に従って，ヒト及び毒性試験で用いた動物種での M10 の血漿中暴露量を比較することで，レンボレキサントを用いた非臨床安全試験において M10 への十分な暴露が達成されているか確認を行った。この M10 の暴露量の比較検討により，レンボレキサントの毒性を評価した（発がん性を含む）少なくとも 1 種の動物種において M10 が毒物学的に適正に評価されていることが示された（2.6.6.9 項，表 2.6.6-25 参照）。

いくつかの脱フッ素代謝物がラット及びサルの排泄物中に検出され，酸化的脱フッ素化がラット及びサルにおけるレンボレキサントの代謝経路の 1 つであることが示された。また，ラットの毒性試験では，フッ素症に関連する骨格及び歯の変化が認められている。追加で実施した毒性試験の結果，レンボレキサントの代謝過程で生じたフッ化物イオンはラットのフッ素症を引き起こすことが明らかになった（2.6.6.8.1 項参照）。一方，ヒトにおいて，脱フッ素代謝物は検出されておらず，レンボレキサントがヒトにおいてフッ素症を引き起こす可能性は低いと考えられた。

代謝物 M4，M9 及び M10 はヒト血漿中で比較的高い暴露量を示すとともに，ヒトオレキシン受容体に対してレンボレキサントと同等の高い結合親和性を有する代謝物である。レンボレキサント及びその代謝物（M4，M9 及び M10）は，OX1R よりも OX2R に対して高い親和性を示すことから，レンボレキサント，M4，M9 及び M10 の血漿中非結合型暴露量及び OX2R に対する in vitro 結合親和性を基に，ヒトにおける睡眠誘発効果への寄与を見積もった。表 2.6.4-47 に示すように，C_{max} 及び AUC ベースでの寄与率は，それぞれレンボレキサントで 62.3%及び 46.7%，M4 で 21.8%及び 28.0%，M9 で 6.8%及び 7.1%，M10 で 9.0%及び 18.2%であった。M4 はこれら代謝物の中で最も高い寄与を示したが，M4 が P-gp 基質であること，又，ラット及びサルにおける M4 の CSF／血漿中非結合型薬物濃度比がレンボレキサントの CSF／血漿中非結合型薬物濃度比よりも少なくとも 2 倍低いことを考慮すると，ヒトにおいて M4 の脳移行性はレンボレキサントの脳移行性よりも低いと考えられた。したがって，レンボレキサント（未変化体）がヒトにおける薬理作用に主に寄与していると考えられ，代謝物の寄与は低いと推察された。

表 2.6.4-47 血漿中濃度及び OX2R に対する in vitro 結合親和性に基づく睡眠誘発作用に対するレンボレキサント及びその代謝物の寄与

Parameters	Unit	Lemborexant	M4	M9	M10
MW	—	410.42	426.42	426.42	426.42
OX2R IC_{50}	(nmol/L)	2.6	3.8	4.7	2.9
$f_{u,p}$ [a]	—	0.113	0.257	0.143	0.085
$C_{max,ss}$	(ng/mL)	59.4	13.9	9.65	13.3
$C_{max,ss,u}$	(nmol/L)	16.4	8.38	3.24	2.65
$C_{max,ss,u}/IC_{50}$	—	6.31	2.21	0.689	0.914
Ratio_$C_{max,ss,u}$	(% of parent)	100	35.0	10.9	14.5
	(% of total)	62.3	21.8	6.8	9.0
$AUC_{(0\text{-}t),ss}$	(ng·h/mL)	431	172	98.0	259
$AUC_{(0\text{-}t),ss,u}$	(nmol·h/L)	119	104	32.9	51.6
$AUC_{(0\text{-}t),ss,u}/IC_{50}$	—	45.8	27.4	7.00	17.8
Ratio_$AUC_{(0\text{-}t),ss,u}$	(% of parent)	100	59.8	15.3	38.9
	(% of total)	46.7	28.0	7.1	18.2

a: For $f_{u,p}$, a value at 100 ng/mL was used.
$AUC_{(0\text{-}t),ss}$ = AUC from zero time to time of last quantifiable concentration at steady state, $AUC_{(0\text{-}t),ss,u}$ = unbound AUC from zero time to time of last quantifiable concentration at steady state, $C_{max,ss}$ = C_{max} at steady state, $C_{max,ss,u}$ = unbound C_{max} at steady state, $f_{u,p}$ = unbound fraction in plasma, IC_{50} = half-maximal inhibitory concentration, OX2R = orexin-2 receptor, MW = molecular weight.
出典：添付資料 4.2.1.1.1 (M10032)，4.2.1.1.6 (M13009)，5.3.2.1.1 (12-304)，5.3.2.1.2 (16-559) 及び 5.3.3.1.3 (E2006-A001-003)

レンボレキサントのエナンチオマーもジアステレオマーもヒトの生体試料中には認められず，レンボレキサントの立体異性体への変換はヒトでは生じないことが示唆された。

In vitro 代謝試験により，レンボレキサントが主に CYP3A によって代謝されることが示された。また，臨床薬物相互作用試験（外国 004 試験［E2006-A001-004，5.3.3.4.1］及び外国 012 試験［E2006-A001-012，5.3.3.4.4］，2.7.2.2.2.4 項参照）において，強力な CYP3A 阻害剤であるイトラコナゾール又は中等度の CYP3A 阻害剤であるフルコナゾールの反復投与との併用によって，レンボレキサントの $AUC_{(0\text{-}inf)}$及び C_{max} の中程度の増加が認められ，強力な CYP3A 誘導剤であるリファンピシンの反復投与との併用によって，レンボレキサントの $AUC_{(0\text{-}inf)}$及び C_{max} の顕著な減少が認められている。これらの知見は，in vitro 代謝試験の結果と一致していた。レンボレキサントは，P-gp，BCRP，OATP1B1 又は OATP1B3 の基質ではないことから，これらのトランスポーターの阻害に起因する DDI の可能性は低いと考えられる。In vitro 試験により，レンボレキサント及びその代謝物（M4，M9 及び M10）は，CYP3A を阻害又は誘導し，CYP2B6 を誘導する可能性が示唆された。そのため，臨床薬物相互作用試験で精査した結果，MRHD（10 mg）において，レンボレキサントの反復投与は典型的な CYP3A 基質であるミダゾラムの血漿中暴露量に影響を与えず，CYP2B6 基質である *S*-ブプロピオンの $AUC_{(0\text{-}inf)}$及び C_{max} を減少させ，*S*-ブプロピオンに対するブプロピオンの[*S,S*]-ヒドロキシ代謝物の $AUC_{(0\text{-}t)}$比を増加させた。したがって，レンボレキサントは MRHD（10 mg）において，CYP3A に対して阻害作用も誘導作用も示さないが，CYP2B6 の弱い誘導剤となる可能性が示された。2.6.4.7 項で説明したように，MRHD（10 mg）での血漿中濃度を考慮すると，レンボレキサント及びその代謝物（M4，M9 及び M10）は，CYP1A2 の誘導，又は他の CYP 分子種及び検討したトランスポーター（OATP1A1，

OATP1B3，MATE1，MATE2-K，OAT1，OAT3 及び OCT2）に対する阻害による DDI を引き起こさないと考えられた。

以上，これらの試験結果は，動物におけるレンボレキサントの薬物動態特性，代謝の動物種差並びにヒトにおける薬物代謝酵素及び薬物トランスポーターを介した薬物間相互作用の可能性を評価する上で適切であり，十分なものであると考える。

2.6.4.10 図表

本文中の図表は，本文中の適切な場所に記載した。

2.6.4.11 参考文献

該当なし。

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2.6.5 薬物動態試験概要表
2.6.5.1 薬物動態試験：一覧表

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Analytical Methods and Validation Reports						
LC-MS/MS method for lemborexant and its metabolites in plasma	No	Rats, Monkeys	in vitro	[redacted]	16-558	4.2.2.1.1
LC-MS/MS method for lemborexant in plasma	No	Rats	in vitro	Eisai Co., Ltd.	S10111	4.2.2.1.2
LC-MS/MS method for lemborexant in plasma	No	Rats	in vitro	Eisai Co., Ltd.	T12019	4.2.2.1.3
LC-MS/MS method for lemborexant in plasma	No	Monkeys	in vitro	Eisai Co., Ltd.	S10112	4.2.2.1.4
LC-MS/MS method for lemborexant in plasma	No	Monkeys	in vitro	Eisai Co., Ltd.	T12020	4.2.2.1.5
LC-MS/MS method for lemborexant in plasma	No	Monkeys	in vitro	Eisai Co., Ltd.	T13011	4.2.2.1.6
LC-MS/MS method for lemborexant in plasma	No	Mice	in vitro	Eisai Co., Ltd.	T14046	4.2.2.1.7
LC-MS/MS method for lemborexant in plasma	No	Rabbits	in vitro	Eisai Co., Ltd.	T12024	4.2.2.1.8
Synthesis of [^{14}C]lemborexant	No	Chemical synthesis	NA	[redacted]	13-143-a	4.2.2.1.9
Purity measurement of [^{14}C]lemborexant	No	Chemical synthesis	NA	[redacted]	13-143-b	4.2.2.1.10
Purification of [^{14}C]lemborexant	No	Chemical synthesis	NA	[redacted]	16-563	4.2.2.1.11

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Absorption After a Single Dose						
Single-dose pharmacokinetics of lemborexant	No	Rats	IV, PO	[redacted]	16-561	4.2.2.2.1
Single-dose toxicokinetics of lemborexant	Yes	Rats	PO	Eisai Co., Ltd.	S10120	4.2.3.1.2
Single-dose pharmacokinetics of lemborexant	No	Monkeys	IV, PO	[redacted]	16-562	4.2.2.2.2
Single-dose toxicokinetics of lemborexant	Yes	Monkeys	PO	Eisai Co., Ltd.	S10118	4.2.3.1.3
Single-dose pharmacokinetics of radioactivity	No	Rats	PO	[redacted]	14-074	4.2.2.3.1
Single-dose pharmacokinetics of radioactivity	No	Monkeys	PO	[redacted]	14-075	4.2.2.3.2
Single-dose pharmacokinetics of radioactivity	No	Rats (pigmented)	PO	[redacted]	14-188	4.2.2.3.3
Absorption After Repeated Dose						
Repeated-dose pharmacokinetics (toxicokinetics, 4 weeks)	Yes	Mice	PO	Sunplanet Co., Ltd.	K14035	4.2.3.2.3
Repeated-dose pharmacokinetics (toxicokinetics, 7 days)	No	Rats	PO	Eisai Co., Ltd.	S10043	4.2.3.2.4
Repeated-dose pharmacokinetics (toxicokinetics, 4 weeks)	Yes	Rats	PO	Sunplanet Co., Ltd.	K11004	4.2.3.2.5
Repeated-dose pharmacokinetics (toxicokinetics, 13 and 26 weeks)	Yes	Rats	PO	Sunplanet Co., Ltd.	K12033	4.2.3.2.8
Repeated-dose pharmacokinetics (toxicokinetics, 4 weeks)	Yes	Monkeys	PO	[redacted]	SBL038-055	4.2.3.2.9

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Repeated-dose pharmacokinetics (toxicokinetics, 13 weeks)	Yes	Monkeys	PO	[redacted]	SBL038-067	4.2.3.2.10
Repeated-dose pharmacokinetics (toxicokinetics, 39 weeks)	Yes	Monkeys	PO	[redacted]	6700074	4.2.3.2.11
Organ Distribution						
CSF to unbound plasma concentration ratio	No	Rats	PO	[redacted]	16-561	4.2.2.2.1
CSF to unbound plasma concentration ratio	No	Monkeys	PO	[redacted]	16-562	4.2.2.2.2
Single-dose tissue distribution of radioactivity	No	Rats	PO	[redacted]	14-074	4.2.2.3.1
Single-dose tissue distribution of radioactivity	No	Monkeys	PO	[redacted]	14-075	4.2.2.3.2
Single-dose tissue distribution of radioactivity	No	Rats (pigmented)	PO	[redacted]	14-188	4.2.2.3.3
Plasma Protein Binding						
Plasma protein binding of lemborexant	No	Mice, Rats, Monkeys, Humans	in vitro	[redacted]	12-304	5.3.2.1.1
Plasma protein binding of lemborexant metabolites	No	Mice, Rats, Monkeys, Humans	in vitro	[redacted]	16-559	5.3.2.1.2
Binding to serum protein	No	Humans	in vitro	Eisai Co., Ltd.	DMPKT2017-003	5.3.2.1.3

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Study in Pregnant or Nursing Animals (Placental Transfer and Excretion Into the Milk)						
Placental transfer of radioactivity	No	Rats (pregnant)	PO	[redacted]	AE-7524-G	4.2.2.3.4
Excretion of radioactivity into the milk	No	Rats (lactating)	PO	[redacted]	AE-7524-G	4.2.2.3.4
Other Distribution Study						
Blood to plasma concentration ratio of lemborexant and its metabolites	No	Mice, Rats, Monkeys, Humans	in vitro	[redacted]	16-560	5.3.2.3.1
Metabolism In Vitro						
Metabolism by liver microsomes and rCYP3A	No	Mice, Rats, Monkeys, Humans	in vitro	Eisai Co., Ltd.	C12062	5.3.2.2.1
CYP isoforms for lemborexant metabolism	No	Humans	in vitro	Eisai Co., Ltd.	DMPKT2012-005	5.3.2.2.2
CYP isoforms for metabolism of lemborexant metabolites	No	Humans	in vitro	Eisai Co., Ltd.	DMPKT2013-011	5.3.2.2.3
Metabolic enzymes for lemborexant metabolism	No	Humans	in vitro	Eisai Co., Ltd.	DMPKT2017-002	5.3.2.2.4
Metabolism by rat liver S9	No	Rats	in vitro	Eisai Co., Ltd.	DMPKT2011-014	4.2.2.4.3
Metabolism In Vivo						
Metabolites in plasma, blood cell, tissues, urine, bile, and feces	No	Rats	PO	[redacted]	AE-7077-G	4.2.2.4.1
Metabolites in plasma, blood cell, urine, and feces	No	Monkeys	PO	[redacted]	AE-7078-G	4.2.2.4.2

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Metabolites in plasma, urine, and feces	No	Humans	PO	[redacted]	AE-7433-G	5.3.2.2.11
Metabolites in plasma	No	Rats, Monkeys, Humans	PO	Eisai Co., Ltd.	DMPKT2013-005	5.3.2.2.6
Metabolites in plasma	No	Humans	PO	Eisai Co., Ltd.	DMPKT2013-009	5.3.2.2.7
Metabolites in plasma and urine	No	Humans	PO	Eisai Co., Ltd.	DMPKT2012-008	5.3.2.2.5
Induction/Inhibition of Drug Metabolizing Enzymes						
Inhibition of CYPs by lemborexant	No	Humans	in vitro	Eisai Co., Ltd.	DMPKT2012-001	5.3.2.2.8
Inhibition of CYPs by lemborexant metabolites	No	Humans	in vitro	[redacted]	B130772	5.3.2.2.9
Induction of CYPs by lemborexant and its metabolites	No	Humans	in vitro	[redacted]	15-131	5.3.2.2.10
Excretion						
Single-dose excretion of radioactivity	No	Rats	PO	[redacted]	14-074	4.2.2.3.1
Single-dose excretion of radioactivity	No	Monkeys	PO	[redacted]	14-075	4.2.2.3.2
Excretion Into Bile						
Single-dose excretion of radioactivity	No	Rats	PO	[redacted]	14-074	4.2.2.3.1
Drug-Drug Interactions (Pharmacokinetic)						
NA						

Test Article: lemborexant

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Study Number	CTD Location
Other Pharmacokinetic Studies						
Substrate susceptibility and inhibitory effects of lemborexant and its metabolites to P-gp and BCRP	No	Humans	in vitro	Eisai Co., Ltd.	DMPKT2013-010	5.3.2.3.2
Inhibitory effect of lemborexant and its metabolites with BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2-K	No	Humans	in vitro	[redacted]	KAC36-02-130827	5.3.2.3.3
Substrate susceptibility of lemborexant and its metabolites to OATP1B1 and OATP1B3	No	Humans	in vitro	[redacted]	KAC37-03-130827	5.3.2.3.4

BCRP = breast cancer resistance protein, BSEP = bile salt export pump, CSF = cerebrospinal fluid, CTD = Common Technical Document, CYP = cytochrome P450, GLP = Good Laboratory Practice, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, MATE = multidrug and toxin extrusion, NA = not applicable, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter, rCYP = recombinant human CYP, P-gp = P-glycoprotein, PO = oral, S9 = 9000×g supernatant of homogenate (subcellular fraction containing microsomes and cytosol).

a: An entry of "Yes" indicates that the study includes a GLP compliance statement.

2.6.5.2 分析方法及びバリデーション試験

Test Article: lemborexant, M4, M9, M10

Study Number/Location in CTD		**16-558/4.2.2.1.1**			
Species/Strain		Rat/Sprague Dawley			
Sample Matrix/Sample Volume		Plasma/50 µL			
Extraction Method / Assay		Solid phase extraction[a] / LC-MS/MS			
Analyte		Lemborexant[b]	M4[b]	M9[b]	M10[b]
IS		ER-571799-00	ER-608441-00	ER-608440-00	ER-608442-00
Quantification Range (ng/mL)		0.3 to 300	0.3 to 300	0.3 to 300	0.3 to 300
Calibration Curve	Accuracy (%)	–7.2 to 7.2	–7.7 to 10.5	–8.1 to 6.9	–8.7 to 8.1
	r	≥0.9986	≥0.9975	≥0.9985	≥0.9978
Intra-Assay	Accuracy (%)	Within ±8.6	Within ±6.9	Within ±7.5	Within ±7.5
	Precision (%)	≤5.4	≤10.4	≤11.2 (LLQC: 16.5)	≤4.4
Inter-Assay	Accuracy (%)	Within ±5.9	Within ±8.2	Within ±6.2	Within ±7.1
	Precision (%)	≤3.9 (LLQC: 17.9)	≤11.3 (LLQC: 15.3)	≤5.6 (LLQC: 15.8)	≤7.1 (LLQC: 19.9)
Recovery	Analyte (%)	91.1 to 98.7	93.8 to 96.3	92.5 to 96.1	90.4 to 98.0
	IS (%)	90.3	97.5	91.4	93.3
Stability	Processed samples at 4 °C	7 days	7 days	7 days	7 days
	Plasma samples at rt	24 hours	24 hours	24 hours	24 hours
	Plasma samples at –15 °C or below	36 days	36 days	36 days	36 days
	Freeze / Thaw cycle	3 cycles	3 cycles	3 cycles	3 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLQC = quality control at lower limit of quantitation, r = correlation coefficient, rt = room temperature.

a: Extraction using OASIS HLB µElution plate.

b: The bioanalytical method for the simultaneous determination of lemborexant, M4, M9, and M10 was used.

Additional Information: No interfering peaks were observed at the retention times of analyte and IS on the chromatograms of rat blank plasma samples.

2.6.5.2 分析方法及びバリデーション試験（続き）

Test Article: lemborexant, M4, M9, M10

Study Number/Location in CTD		**16-558/4.2.2.1.1**			
Species/Strain		Monkey/Cynomolgus			
Sample Matrix/Sample Volume		Plasma/50 µL			
Extraction Method / Assay		Solid phase extraction[a] / LC-MS/MS			
Analyte		Lemborexant[b]	M4[b]	M9[b]	M10[b]
IS		ER-571799-00	ER-608441-00	ER-608440-00	ER-608442-00
Quantification Range (ng/mL)		0.3 to 300	0.3 to 300	0.3 to 300	0.3 to 300
Calibration Curve	Accuracy (%)	–3.9 to 5.4	–9.7 to 8.3	–7.9 to 5.5	–6.1 to 6.2
	r	≥0.9994	≥0.9985	≥0.9988	≥0.9989
Intra-Assay	Accuracy (%)	Within ±8.0	Within ±4.8	Within ±11.6	Within ±2.9
	Precision (%)	≤11.3	≤7.2	≤5.7	≤5.6
Inter-Assay	Accuracy (%)	Within ±2.2	Within ±5.9	Within ±3.8	Within ±4.9
	Precision (%)	≤3.9 (LLQC: 16.2)	≤12.8	≤4.9 (LLQC: 17.7)	≤6.1
Recovery	Analyte (%)	93.4 to 97.3	92.6 to 95.9	94.9 to 98.6	95.2 to 96.2
	IS (%)	95.5	90.5	90.9	92.7
Stability	Processed samples at 4 °C	7 days	7 days	7 days	7 days
	Plasma samples at rt	24 hours	24 hours	24 hours	24 hours
	Plasma samples at –15 °C or below	36 days	36 days	36 days	36 days
	Freeze / Thaw cycle	3 cycles	3 cycles	3 cycles	3 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LLQC = quality control at lower limit of quantitation, r = correlation coefficient, rt = room temperature.

a: Extraction using OASIS HLB µElution plate.

b: The bioanalytical method for the simultaneous determination of lemborexant, M4, M9, and M10 was used.

Additional Information: No interfering peaks were observed at the retention times of analyte and IS on the chromatograms of monkey blank plasma samples.

2.6.5.2 分析方法及びバリデーション試験（続き）

Study Number/Location in CTD		**T14046/4.2.2.1.7**	**S10111/4.2.2.1.2, T12019/4.2.2.1.3**	**T12024/4.2.2.1.8**	**S10112/4.2.2.1.4 T12020/4.2.2.1.5**	**T13011/4.2.2.1.6**
Species/Strain		Mouse/CB6F1	Rat/Sprague Dawley	Rabbit/NZW	Monkey/Cynomolgus	Monkey/Rhesus
Analyte		Lemborexant	Lemborexant	Lemborexant	Lemborexant	Lemborexant
Sample Matrix/Sample Volume		Plasma/25 µL	Plasma/50 µL	Plasma/50 µL	Plasma/50 µL	Plasma/50 µL
Extraction Method		Protein precipitation by acetonitrile/methanol (1/1, v/v)	Protein precipitation by acetonitrile/methanol (1/1, v/v)	Protein precipitation by acetonitrile/methanol (1/1, v/v)	Protein precipitation by acetonitrile/methanol (1/1, v/v)	Protein precipitation by acetonitrile/methanol (1/1, v/v)
Assay		LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
IS		ER-571799-00	ER-571799-00	ER-571799-00	ER-571799-00	ER-571799-00
Quantification Range (ng/mL)		2 to 2000	1 to 1000	1 to 1000	1 to 1000	1 to 1000
Calibration Curve: Accuracy (%)		–7.0 to 3.8	–8.0 to 14.0	–5.5 to 3.6	–6.2 to 10.5	–6.6 to 5.0
Intra-Assay	Accuracy (%)	–4.8 to –0.9	–7.5 to –3.3	–4.7 to 4.0	–9.8 to –1.5	–7.3 to 1.0
	Precision (%)	≤3.4	≤2.2	≤2.3	≤3.9	≤1.1
Inter-Assay	Accuracy (%)	–4.2 to 1.2	–5.3 to 0.1	–5.6 to 0.8	–6.2 to 1.5	–7.7 to 0.5
	Precision (%)	≤3.0	≤5.9	≤4.4	≤2.2	≤2.7
Recovery	Lemborexant (%)	105.1 to 107.7	120.8 to 139.7	NA	123.0 to 143.9	NA
	IS (%)	106.3	136.5	NA	139.6	NA
Stability	Processed samples at 2 to 8 °C	7 days	7 days	7 days	7 days	7 days
	Plasma samples at rt	24 hours	22 hours	24 hours	22 hours	24 hours
	Plasma samples below –15 °C	4 weeks	4 weeks	4 weeks	4 weeks	2 weeks
	Freeze / Thaw cycle	3 cycles	3 cycles	3 cycles	3 cycles	3 cycles

CTD = Common Technical Document, IS = internal standard, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, NZW = New Zealand White, rt = room temperature.

Additional Information: No interfering peaks were observed at the retention times of lemborexant and IS on the chromatograms of blank plasma samples from all species.

2.6.5.3 薬物動態試験：吸収：単回投与

Test Article: lemborexant

Rats **Study Number: 16-561** **Location in CTD: 4.2.2.2.1**

Strain/Gender/Number of Animals		Sprague Dawley/Male/4							
Feeding Condition		Fasted							
Vehicle / Formulation		200 mmol/L hydrochloric acid / Solution							
Method of Administration		IV and PO							
Dose		IV: 0.3 and 1 mg/kg, PO: 10, 30, and 100 mg/kg							
Sample/Analyte / Assay		Plasma/Lemborexant, M4, M9, M10 / LC-MS/MS							
Dosing Route	**Lemborexant Dose (mg/kg)**	**Analyte**	**$AUC_{(0\text{-}inf)}$ (ng·h/mL)**	**CL (mL/h/kg)**	**V_{ss} (L/kg)**	**$t_{1/2}$ (h)**	**C_{max} (ng/mL)**	**t_{max} (h)**	**F (%)**
IV	0.3	Lemborexant	110	2730	4.21	1.61	NA	NA	NA
	1		353	2870	3.40	1.64	NA	NA	NA
PO	10		87.8	NA	NA	1.49	50.0	0.25	2.5
	30		1160	NA	NA	2.65	452	1.00	11.0
	100		7970	NA	NA	2.24	964	4.50	22.6
IV	0.3	M4	NC	NA	NA	NC	NA	NA	NA
	1		NC	NA	NA	NC	NA	NA	NA
PO	10		5.74	NA	NA	0.682	4.73	0.25	NA
	30		92.4	NA	NA	1.33	36.6	1.00	NA
	100		506	NA	NA	2.14	66.7	0.50	NA

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Test Article: lemborexant

Rats **Study Number: 16-561** **Location in CTD: 4.2.2.2.1**

Dosing Route	Lemborexant Dose (mg/kg)	Analyte	$AUC_{(0\text{-}inf)}$ (ng·h/mL)	CL (mL/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	F (%)
IV	0.3	M9	8.02	NA	NA	2.24	NA	NA	NA
	1		26.4	NA	NA	2.23	NA	NA	NA
PO	10		357	NA	NA	1.73	182	0.75	NA
	30		1670	NA	NA	1.53	623	1.00	NA
	100		11,200	NA	NA	1.56	1410	1.00	NA
IV	0.3	M10	NC	NA	NA	NC	NA	NA	NA
	1		NC	NA	NA	NC	NA	NA	NA
PO	10		NC	NA	NA	NC	NC	NC	NA
	30		NC	NA	NA	NC	1.63	1.00	NA
	100		20.5[a]	NA	NA	1.70[a]	3.05	0.50	NA

The mean of 4 individual values is presented for the pharmacokinetic parameters except t_{max} and F value. For t_{max} values, the median for 4 individual values is presented. F values were calculated based on the $AUC_{(0\text{-}inf)}$ values at 1 mg/kg IV, and those were calculated using the mean $AUC_{(0\text{-}inf)}$ values.

$AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, CL = total plasma clearance, CSF = cerebrospinal fluid, CTD = Common Technical Document, F = absolute bioavailability, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, NC = not calculated, PO = oral, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life, V_{ss} = volume of distribution at steady state.

a: The mean of 2 individual values is presented.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. 16-558). Lemborexant and its metabolites (M4, M9, and M10) showed rapid distribution to the brain in rats. At 2 hours postdose or later (100 mg/kg), the CSF to unbound plasma concentration ratio of lemborexant was approximately 2- to 4-fold higher than those of M4 and M10 and comparable to that of M9. These results suggested that M4 and M10 had lower brain penetration than lemborexant in rats (Section 2.6.5.5).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: lemborexant

Rats (Toxicokinetics in an Extended Single Oral Dose Toxicology Study) **Study Number: S10120** **Location in CTD: 4.2.3.1.2**

Strain/Gender/Number of Animals	Sprague Dawley/Male and female/4					
Feeding Condition	Non-fasted					
Vehicle / Formulation	Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration	Oral					
Dose	100, 300, and 1000 mg/kg					
Sample/Analyte / Assay	Plasma/Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters	**Male**			**Female**		
	100 mg/kg	**300 mg/kg**	**1000 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
t_{max} (h)	1.5 (1 – 2)	6 (4 – 8)	6 (4 – 24)	2 (1 – 2)	6 (2 – 24)	24 (24 – 24)
C_{max} (ng/mL)	2460±363	2720±592	3308±1363	3312±535	2948±1269	7332±1114
$AUC_{(0-24)}$ (ng·h/mL)	11,028±1908	28,639±7030	47,016±24,772	19,672±2129	42,864±16,287	95,753±23,348

C_{max} and $AUC_{(0-24)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals.

$AUC_{(0-24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. S10111). C_{max} in males was similar in all dose groups. On the other hand, C_{max} in females was similar at 100 and 300 mg/kg, and increased less than dose proportionally from 300 to 1000 mg/kg. $AUC_{(0-24)}$ in males and females increased less than dose proportionally from 100 to 1000 mg/kg.

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: [^{14}C]lemborexant

Rats **Study Number: 14-074** **Location in CTD: 4.2.2.3.1**

Strain/Gender/Number of Animals	Sprague Dawley/Male/3
Feeding Condition	Fasted[a]
Vehicle / Formulation	100 mmol/L hydrochloric acid / Solution
Method of Administration / Dose	Oral, by using a polypropylene syringe with a gavage needle / 10 mg/kg
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (K0110-030)
Sample/Analyte/Assay	Blood/Radioactivity/Liquid scintillation counting
Pharmacokinetic Parameters	**Oral, 10 mg/kg**
C_{max} (ng eq./mL)	1085.6±283.3
t_{max} (h)	0.83±0.17
$t_{1/2}$ (h)	110±10
$AUC_{(0-t)}$ (ng eq.·h/mL)	8930±1240
$AUC_{(0-inf)}$ (ng eq.·h/mL)	11,800±1300

Concentration of radioactivity was expressed as the equivalent of lemborexant (ng eq./mL), and related parameters were calculated. Each parameter represents the mean ±SEM of 3 animals.

$AUC_{(0-inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0-t)}$ = AUC from zero time to time of last quantifiable concentration, CTD = Common Technical Document, eq. = equivalent, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life.

a: The fasting of the animals was started at 17:30 to 18:30 on the day before dosing (at least 16 hours before dosing) and terminated at 6 hours after administration. Water was given freely.

Additional Information: This study also investigated the distribution of radioactivity in organs and tissues (Section 2.6.5.5), the excretion of radioactivity in urine and feces (Section 2.6.5.13), and the biliary excretion of radioactivity (Section 2.6.5.14).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: [^{14}C]lemborexant

Rats (Pigmented) **Study Number: 14-188** **Location in CTD: 4.2.2.3.3**

Strain/Gender/Number of Animals	Brown Norway/Male/3
Feeding Condition	Fasted[a]
Vehicle / Formulation	100 mmol/L hydrochloric acid / Solution
Method of Administration / Dose	Oral, by using a polypropylene syringe with a gavage needle / 10 mg/kg
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (K0110-030)
Sample/Analyte/Assay	Blood/Radioactivity/Liquid scintillation counting
Pharmacokinetic Parameters	**Oral, 10 mg/kg**
C_{max} (ng eq./mL)	923.0±61.4
t_{max} (h)	1.00±0.00
$t_{1/2}$ (h)	67.8±7.8
$t_{1/2}$ (day)	2.83±0.32
$AUC_{(0-t)}$ (ng eq.·h/mL)	8670±620
$AUC_{(0-inf)}$ (ng eq.·h/mL)	10,700±800

Concentration of radioactivity was expressed as the equivalent of lemborexant (ng eq./mL), and related parameters were calculated. Each parameter represents the mean ±SEM of 3 animals.

$AUC_{(0-inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0-t)}$ = AUC from zero time to time of last quantifiable concentration, CTD = Common Technical Document, eq. = equivalent, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life.

a: The fasting of the animals was started at 17:30 or 18:00 on the day before dosing (at least 16 hours before dosing) and terminated at 6 hours after administration. Water was given freely.

Additional Information: This study also investigated the distribution of radioactivity in organs and tissues (Section 2.6.5.5).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: lemborexant

Monkeys **Study Number: 16-562** **Location in CTD: 4.2.2.2.2**

Strain/Gender/Number of Animals	Cynomolgus/Male/4								
Feeding Condition	Fasted								
Vehicle / Formulation	200 mmol/L hydrochloric acid / Solution								
Method of Administration	IV and PO								
Dose	IV: 0.3 and 1 mg/kg, PO: 1, 3, and 10 mg/kg								
Sample/Analyte / Assay	Plasma/Lemborexant, M4, M9, M10 / LC-MS/MS								
Dosing Route	**Lemborexant Dose (mg/kg)**	**Analyte**	**$AUC_{(0\text{-}inf)}$ (ng·h/mL)**	**CL (mL/h/kg)**	**V_{ss} (L/kg)**	**$t_{1/2}$ (h)**	**C_{max} (ng/mL)**	**t_{max} (h)**	**F (%)**
IV	0.3	Lemborexant	251	1210	4.73	6.25	NA	NA	NA
	1		852	1190	3.31	5.16	NA	NA	NA
PO	1		169	NA	NA	3.78	61.7	1.50	19.8
	3		420	NA	NA	5.23	110	1.00	16.1
	10		2020	NA	NA	5.10	660	1.50	23.4
IV	0.3	M4	35.5	NA	NA	2.78	NA	NA	NA
	1		170	NA	NA	3.40	NA	NA	NA
PO	1		151	NA	NA	1.49	58.9	1.50	NA
	3		361	NA	NA	2.48	107	1.00	NA
	10		1670	NA	NA	4.31	492	2.00	NA

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Test Article: lemborexant

Monkeys **Study Number: 16-562** **Location in CTD: 4.2.2.2.2**

Dosing Route	Lemborexant Dose (mg/kg)	Analyte	$AUC_{(0\text{-}inf)}$ (ng·h/mL)	CL (mL/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	F (%)
IV	0.3	M9	NC	NA	NA	NC	NA	NA	NA
	1		8.85	NA	NA	3.70	NA	NA	NA
PO	1		22.0[a]	NA	NA	2.24[a]	6.14	1.50	NA
	3		44.7	NA	NA	2.74	12.0	1.00	NA
	10		231	NA	NA	5.13	84.1	1.50	NA
IV	0.3	M10	8.89	NA	NA	7.64	NA	NA	NA
	1		21.6	NA	NA	1.80	NA	NA	NA
PO	1		29.6	NA	NA	1.23	12.6	1.50	NA
	3		59.2	NA	NA	1.74	17.9	1.50	NA
	10		238	NA	NA	1.95	65.3	2.00	NA

The mean of 4 individual values are presented for the pharmacokinetic parameters except t_{max}. For t_{max} values, the median for 4 individual values is presented. F values were calculated based on the individual $AUC_{(0\text{-}inf)}$ values at 1 mg/kg IV, and those were calculated using the individual $AUC_{(0\text{-}inf)}$ values.

$AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, CL = total plasma clearance, CSF = cerebrospinal fluid, CTD = Common Technical Document, F = absolute bioavailability, IV = intravenous, LC-MS/MS = liquid chromatography with tandem mass spectrometry, NA = not applicable, NC = not calculated, PO = oral, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life, V_{ss} = volume of distribution at steady state.

a: n=2.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. 16-558). At 8 hours postdose (10 mg/kg), the CSF to unbound plasma concentration ratio of lemborexant was approximately 2-fold higher than those of M4 and M9, and comparable to that of M10. These results suggested that M4 and M9 had lower brain penetration than lemborexant at steady state in monkeys (Section 2.6.5.5).

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: lemborexant

Monkeys (Toxicokinetics in an Extended Single Oral Dose Toxicology Study) **Study Number: S10118** **Location in CTD: 4.2.3.1.3**

Strain/Gender/Number of Animals	Cynomolgus /Male and female/3 or 5					
Feeding Condition	Non-fasted					
Vehicle / Formulation	Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration	Oral					
Dose	100, 300, and 1000 mg/kg					
Sample/Analyte / Assay	Plasma/Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters	**Male**			**Female**		
	100 mg/kg	**300 mg/kg**	**1000 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
t_{max} (h)	4 (2 – 4)	24 (4 – 24)	24 (8 – 24)	4 (4 – 4)	24 (4 – 24)	24 (0.5 – 24)
C_{max} (ng/mL)	3166±553	3839±1613	5859±1851	4298±1618	4488±1034	4890±2121
$AUC_{(0-24)}$ (ng·h/mL)	46,688±11,978	68,057±33,287	96,718±25,167	54,783±29,810	82,771±29,800	85,200±39,271

C_{max} and $AUC_{(0-24)}$ represent the mean ±SD of 3 animals (100 and 300 mg/kg) or 5 animals (1000 mg/kg) and t_{max} represents the median and range of 3 animals (100 and 300 mg/kg) or 5 animals (1000 mg/kg).

$AUC_{(0-24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. S10112). C_{max} and $AUC_{(0-24)}$ in males and females increased less than dose proportionally from 100 to 1000 mg/kg.

2.6.5.3 薬物動態試験：吸収：単回投与（続き）

Test Article: **[^{14}C]lemborexant**

Monkeys **Study Number: 14-075** **Location in CTD: 4.2.2.3.2**

Strain/Gender/Number of Animals	Cynomolgus/Male/3		
Feeding Condition	Fasted[a]		
Vehicle / Formulation	100 mmol/L hydrochloric acid / Solution		
Method of Administration / Dose	Oral, by using a polypropylene syringe with catheter / 3 mg/kg		
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (K0110-030)		
Sample/Analyte/Assay	Blood, Plasma, Blood Cells/Radioactivity/Liquid scintillation counting		
Pharmacokinetic Parameters	**Blood**	**Plasma**	**Blood Cells**
C_{max} (ng eq./mL)	608.9±105.4	706.0±128.8	529.2±127.2
t_{max} (h)	1.8±1.1	1.8±1.1	1.2±0.4
$t_{1/2}$ (h)	110±10	110±0	110±20
$AUC_{(0-t)}$ (ng eq.·h/mL)	8140±370	5800±680	10,800±1500
$AUC_{(0-inf)}$ (ng eq.·h/mL)	9030±470	6640±700	11,900±1800

Concentration of radioactivity was expressed as the equivalent of lemborexant (ng eq./mL), and related parameters were calculated. Each parameter represents the mean ±SEM of 3 animals.

$AUC_{(0-inf)}$ = AUC from zero time extrapolated to infinite time, $AUC_{(0-t)}$ = AUC from zero time to time of last quantifiable concentration, CTD = Common Technical Document, eq. = equivalent, t_{max} = time at which the highest drug concentration occurs, $t_{1/2}$ = terminal elimination phase half-life.

a: The fasting of the animals was started from 18:00 on the day before the dosing (at least 16 hours before dosing) to 6 hours after the dosing. Water was given freely.

Additional Information: This study also investigated the distribution of radioactivity in organs and tissues (Section 2.6.5.5) and the excretion of radioactivity in urine and feces (Section 2.6.5.13).

2.6.5.4 薬物動態試験：吸収：反復投与

Test Article: lemborexant

Mice (toxicokinetics, 4 weeks)　　**Study Number: K14035**　　**Location in CTD: 4.2.3.2.3**

Strain/Gender/Number of Animals		CB6F1-nonTg rasH2/Male and female/4 per time point					
Feeding Condition		Diet: Solid chow, ad libitum. Water: Sterilized tap water available ad libitum.					
Vehicle/Formulation		Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration		Oral by gavage					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 4 weeks/100, 300, or 1000					
Sample/Assay date		Plasma/Day 28					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**1000 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 28**	1117	1460	3628	1826	1946	5026
$AUC_{(0-24)}$ (ng·h/mL)	**Day 28**	8299	20,692	52,509	18,328	27,272	55,877
t_{max} (h)	**Day 28**	4	4	8	2	8	4

The values were obtained from the mean concentration of 4 animals/time point.

$AUC_{(0-24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. T14046). The sex related-differences in C_{max} and $AUC_{(0-24)}$ were within 2.2-fold. The C_{max} and $AUC_{(0-24)}$ increased less than dose proportionally from 100 to 1000 mg/kg.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: lemborexant

Rats (toxicokinetics, 7 days)　　**Study Number: S10043**　　**Location in CTD: 4.2.3.2.4**

Strain/Gender/Number of Animals		Sprague Dawley/Male and female/3					
Feeding Condition		Diet: Solid chow, approximately 21 g/day in males and 14 g/day in females. Water: Sterilized tap water available ad libitum.					
Vehicle/Formulation		0.5% methylcellulose solution/Suspension					
Method of Administration		Oral by gavage					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 7 days/100, 300, or 1000					
Sample/Assay date		Plasma/Days 1 and 7					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		100 mg/kg	**300 mg/kg**	**1000 mg/kg**	**100 mg/kg**	**300 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 1**	98.1±40.4	800.0±970.5	1018.7±769.5	617.1±196.9	1161.1±429.6	2037.2±204.1
	Day 7	347.1±226.3	983.8±977.8	2844.7±1455.1	762.0±280.4	2670.3±837.3	4509.9±1270.0
$AUC_{(0-24)}$ (ng·h/mL)	**Day 1**	656.8±247.9	4006.4±4373.5	4970.4±2753.4	3384.3±1607.7	11,454.2±3576.4	19,778.0±11,399.1
	Day 7	1815.5±1422.6	5095.8±4564.1	25,538.9±18,700.2	4910.5±2012.5	24,255.7±15,561.5	46,303.5±19,936.0
t_{max} (h)	**Day 1**	4 (2 – 4)	4 (2 – 4)	4 (4 – 4)	2 (2 – 2)	4 (2 – 8)	2 (2 – 4)
	Day 7	2 (2 – 4)	2 (2 – 4)	8 (4 – 8)	4 (2 – 4)	4 (4 – 4)	4 (4 – 4)

C_{max} and $AUC_{(0-24)}$ represent the mean ±SD of 3 animals and t_{max} represents the median and range of 3 animals.

$AUC_{(0-24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs.

Additional Information: There were sex related-differences in C_{max} and $AUC_{(0-24)}$ (female > male). C_{max} and $AUC_{(0-24)}$ increased after repeated administration for 7 days.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: lemborexant

Rats (toxicokinetics, 4 weeks)　　**Study Number: K11004**　　**Location in CTD: 4.2.3.2.5**

Strain/Gender/Number of Animals		Sprague Dawley/Male and female/4					
Feeding Condition		Diet: Solid chow, approximately 21 g/day in males and 14 g/day in females. Water: Sterilized tap water available ad libitum.					
Vehicle / Formulation		Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration		Oral by gavage					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 4 weeks/30, 100, or 1000					
Sample/Assay date		Plasma/Days 1, 8, and 28					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		30 mg/kg	**100 mg/kg**	**1000 mg/kg**	**30 mg/kg**	**100 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 1**	351±216	1762±665	2973±518	1369±391	2537±64	3951±1992
	Day 8	380±72	2235±1091	3727±1994	1409±400	4119±1496	8018±3712
	Day 28	352±66	1792±1186	4222±1191	1867±590	4456±1503	7025±1573
$AUC_{(0\text{-}24)}$ (ng·h/mL)	**Day 1**	824±326	11,094±4802	38,084±17,639	3301±919	18,058±3305	62,795±20,780
	Day 8	1181±245	11,987±4749	44,857±26,190	3130±902	21,333±5925	128,515±114,122
	Day 28	1541±613	13,206±5020	51,901±14,281	3981±1130	25,873±4127	88,431±22,835
t_{max} (h)	**Day 1**	1.5 (1 – 2)	1.5 (1 – 8)	6 (4 – 24)	1 (1 – 1)	2 (1 – 4)	14 (4 – 24)
	Day 8	1.5 (1 – 2)	1.5 (0.5 – 2)	6 (4 – 8)	1 (1 – 1)	1 (1 – 1)	4 (Pre – 8)
	Day 28	1.5 (1 – 2)	1.5 (1 – 4)	8 (4 – 8)	1 (1 – 1)	1 (1 – 4)	4 (4 – 8)

C_{max} and $AUC_{(0\text{-}24)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals.

$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, Pre = pre-dose, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. S10111). C_{max} and $AUC_{(0\text{-}24)}$ increased more than dose proportionally from 30 to 100 mg/kg in both males and females, except C_{max} in females. On the other hand, C_{max} and $AUC_{(0\text{-}24)}$ increased less than dose proportionally from 100 to 1000 mg/kg in both males and females. Sex related-differences in C_{max} and $AUC_{(0\text{-}24)}$ (female > male) were observed, particularly at 30 mg/kg. No apparent changes in C_{max} and $AUC_{(0\text{-}24)}$ after repeated administration for 4 weeks were observed.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: lemborexant

Rats (toxicokinetics, 13 and 26 weeks) **Study Number: K12033** **Location in CTD: 4.2.3.2.8**

Strain/Gender/Number of Animals		Sprague Dawley/Male and female/4					
Feeding Condition		Diet: Solid chow, approximately 21 g/day in males and 14 g/day in females. Water: Sterilized tap water available ad libitum.					
Vehicle / Formulation		Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration		Oral by gavage					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 13 and 26 weeks/30, 100, or 1000					
Sample/Assay date		Plasma/Days 1, 92, and 183					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		30 mg/kg	**100 mg/kg**	**1000 mg/kg**	**30 mg/kg**	**100 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 1**	371±96	1816±875	4151±823	955±213	2711±707	7461±2669
	Day 92	662±226	2650±423	4819±1287	1829±423	3667±952	10,811±5361
	Day 183	690±80	2597±1080	4798±940	1543±488	5230±2041	13,906±4305
$AUC_{(0-24)}$ (ng·h/mL)	**Day 1**	609±52	10,233±5055	67,457±14,948	1886±313	16,661±4774	115,969±36,081
	Day 92	2195±599	21,470±4269	56,749±20,430	5207±1150	21,971±3937	168,962±128,427
	Day 183	2330±649	18,015±8476	60,697±10727	5335±1011	26,486±1798	240,344±69,030
t_{max} (h)	**Day 1**	1 (1 – 1)	2.5 (1 – 4)	6 (4 – 8)	1 (1 – 1)	1 (0.5 – 1)	24 (4 – 24)
	Day 92	1.5 (1 – 2)	2 (1 – 2)	6 (4 – 8)	1 (1 – 1)	1.5 (1 – 4)	6 (4 – 8)
	Day 183	2 (1 – 2)	2 (1 – 2)	8 (8 – 8)	1 (1 – 1)	2 (1 – 2)	8 (Pre – 8)

C_{max} and $AUC_{(0-24)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals.

$AUC_{(0-24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, Pre = pre-dose, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study Nos. S10111 and T12019). There were sex related-differences in C_{max} and $AUC_{(0-24)}$ (female > male). On Day 1, C_{max} and $AUC_{(0-24)}$ in males increased more than doseproportionally from 30 to 100 mg/kg. C_{max} in females increased dose proportionally, but $AUC_{(0-24)}$ increased more than dose proportionally from 30 to 100 mg/kg. C_{max} and $AUC_{(0-24)}$ increased less than dose proportionally from 100 to 1000 mg/kg in both males and females. C_{max} and $AUC_{(0-24)}$ increased after repeated administration, the exception being C_{max} and $AUC_{(0-24)}$ in males at 1000 mg/kg.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: lemborexant

Monkeys (toxicokinetics, 4 weeks) **Study Number: SBL038-055** **Location in CTD: 4.2.3.2.9**

Strain/Gender/Number of Animals		Cynomolgus/Male and female/4					
Feeding Condition		Diet: Approximately 108 g/day of solid food was provided to each animal once daily between 14:30 and 16:00. Water: Available ad libitum.					
Vehicle / Formulation		Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration		Oral by gavage (administered into the stomach via the nasal cavity using a disposable catheter and syringe)					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 4 weeks/30, 100, or 1000					
Sample/Assay date		Plasma/Days 1, 7, and 28					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		30 mg/kg	**100 mg/kg**	**1000 mg/kg**	**30 mg/kg**	**100 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 1**	2249±536	3312±757	3362±1723	1995±495	3878±1656	3226±1608
	Day 7	3635±335	6289±1137	6590±1856	2774±307	4849±2355	7737±4849
	Day 28	3314±642	7165±1553	5611±1793	3031±1664	8500±2705	3945±616
$AUC_{(0-24)}$ (ng·h/mL)	**Day 1**	17,627±3793	43,734±19,606	64,655±36,979	10,537±4242	44,880±22,408	48,143±21,296
	Day 7	29,735±4187	85,738±19,471	106,448±50,167	19,230±3369	55,867±27,080	125,210±97,505
	Day 28	27,335±7829	70,446±30,045	88,409±37,633	18,192±6565	80,856±19,557	39,299±5963
t_{max} (h)	**Day 1**	3 (2 – 4)	6 (2 – 8)	8 (2 – 24)	2 (2 – 4)	4 (2 – 4)	16 (8 – 24)
	Day 7	4 (2 – 4)	4 (4 – 4)	6 (2 – 24)	4 (2 – 4)	4 (4 – 4)	6 (4 – 8)
	Day 28	4 (4 – 4)	4 (1 – 4)	8 (4 – 8)	2 (2 – 2)	4 (4 – 4)	3 (2 – 4)

C_{max} and $AUC_{(0-24)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals.

$AUC_{(0-24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. S10112). C_{max} increased less than dose proportionally from 30 to 100 mg/kg in both males and females, but $AUC_{(0-24)}$ increased dose proportionally. C_{max} and $AUC_{(0-24)}$ in males and females were almost similar in 100 and 1000 mg/kg. No apparent sex-related differences in C_{max} and $AUC_{(0-24)}$ were observed. C_{max} and $AUC_{(0-24)}$ in males and females increased following repeated administration, except the $AUC_{(0-24)}$ at 1000 mg/kg on Day 28.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: lemborexant

Monkeys (toxicokinetics, 13 weeks) **Study Number: SBL038-067** **Location in CTD: 4.2.3.2.10**

Strain/Gender/Number of Animals		Cynomolgus/Male and female/4					
Feeding Condition		Diet: Approximately 108 g/day of solid food was provided to each animal once daily between 14:30 and 16:00. Water: Available ad libitum.					
Vehicle / Formulation		Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration		Oral by gavage (administered into the stomach via the nasal cavity using a disposable catheter and syringe)					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 13 weeks/20, 100, or 1000					
Sample/Assay date		Plasma/Days 1, 28, 56, and 91					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		20 mg/kg	**100 mg/kg**	**1000 mg/kg**	**20 mg/kg**	**100 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 1**	1185±195	3354±989	5906±3389	1070±585	2745±1531	3842±588
	Day 28	2246±504	6444±2408	7223±3731	1761±809	8438±2868	6050±1404
	Day 56	2459±852	6268±2308[a]	9473±5174	2476±879	9978±3223	4756±2075
	Day 91	2655±926	6680±2755[a]	8660±803	2171±728	6871±1126	4887±1787
$AUC_{(0\text{-}24)}$ (ng·h/mL)	**Day 1**	7805±1911	56,623±9291	103,650±59,720	5299±1667	20,705±8197	72,601±17,031
	Day 28	15,524±4367	74,099±40,034	111,759±64,947	11,628±3725	68,539±38,688	94,490±31,867
	Day 56	17,355±4914	69,769±45,930[a]	165,788±78,837	14,667±4965	80,375±33,893	58,294±10,943
	Day 91	19,696±5344	72,183±43,678[a]	132,720±37,601	12,795±3780	56,480±20,783	70,875±23,743
t_{max} (h)	**Day 1**	2 (1 – 4)	6 (2 – 8)	8 (8 – 24)	3 (2 – 4)	2 (2 – 2)	8 (8 – 24)
	Day 28	2 (2 – 4)	2 (2 – 4)	6 (Pre – 8)	4 (2 – 4)	4 (1 – 4)	4 (4 – 8)
	Day 56	3 (2 – 4)	2 (2 – 4)[a]	5 (2 – 24)	3 (2 – 4)	4 (2 – 4)	4 (4 – 4)
	Day 91	3 (2 – 4)	2 (2 – 4)[a]	4 (1 – 8)	2 (2 – 4)	3 (2 – 4)	4 (2 – 8)

Except as noted by footnote a, C_{max} and $AUC_{(0\text{-}24)}$ represent the mean ±SD of 4 animals and t_{max} represents the median and range of 4 animals.
a: 3 animals, 1 animal had no data for death.
$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, Pre = pre-dose, t_{max} = time at which the highest drug concentration occurs.
Additional Information: Quantification was conducted by a validated method described in Section 2.6.5.2 (Study No. S10112). No sex related-differences in C_{max} and $AUC_{(0\text{-}24)}$ were observed. C_{max} increased less than dose proportionally from 20 to 1000 mg/kg in both males and females. $AUC_{(0\text{-}24)}$ in males and females increased dose proportionally from 20 to 100 mg/kg, but increased less than dose proportionally from 100 to 1000 mg/kg. C_{max} and $AUC_{(0\text{-}24)}$ in males and females increased following repeated administration, except $AUC_{(0\text{-}24)}$ in females at 1000 mg/kg on Days 56 and 91.

2.6.5.4 薬物動態試験：吸収：反復投与（続き）

Test Article: lemborexant

Monkeys (toxicokinetics, 39 weeks) **Study Number: 6700074** **Location in CTD: 4.2.3.2.11**

Strain/Gender/Number of Animals		Cynomolgus/Male and female/4					
Feeding Condition		Diet: Food was provided twice daily. Water: Available ad libitum.					
Vehicle / Formulation		Mixture of 0.5% methylcellulose solution and 1 mol/L hydrochloric acid by the ratio of 4:1 / Suspension					
Method of Administration		Oral by gavage (administered using a disposable catheter attached to a plastic syringe)					
Dosing Regimen/ Dose (mg/kg/day)		Once daily for 39 weeks/10, 100, or 1000					
Sample/Assay date		Plasma/Days 1, 85, and 269					
Analyte / Assay		Lemborexant / LC-MS/MS					
Pharmacokinetic Parameters		**Male**			**Female**		
		10 mg/kg	**100 mg/kg**	**1000 mg/kg**	**10 mg/kg**	**100 mg/kg**	**1000 mg/kg**
C_{max} (ng/mL)	**Day 1**	584±406	1880±819	4250±1130	506±194	3780±1630	3640±674
	Day 85	1280±330	5580±1950	5480±3190	763±60.6	6600±2320	4590±1210
	Day 269	960±109	6930±1490	9620±3140	1160±488	8660±2740	6930±3720
$AUC_{(0\text{-}24)}$ (ng·h/mL)	**Day 1**	2850±1770	28,000±13,500	70,700±18,700	2650±691	34,600±14,000	53,500±10,400
	Day 85	6670±1570	48,000±19,400	75,900±48,100	4370±799	54,800±21,100	56,500±26,700
	Day 269	5510±1690	82,900±23,300	155,000±54,800	4970±1390	82,800±34,000	98,200±54,900
t_{max} (h)	**Day 1**	1 (1 – 4)	1 (1 – 4)	8 (8 – 8)	1.5 (1 – 2)	2 (1 – 8)	8 (4 – 24)
	Day 85	1 (1 – 1)	1.5 (1 – 2)	3 (1 – 4)	1.5 (1 – 2)	1.5 (1 – 4)	3 (2 – 8)
	Day 269	1 (1 – 1)	1.5 (1 – 4)	8 (4 – 8)	1 (1 – 1)	1 (1 – 1)	4 (4 – 8)

C_{max} and $AUC_{(0\text{-}24)}$ represent as the mean ±SD of 4 animals and t_{max} represent as the median and range of 4 animals.

$AUC_{(0\text{-}24)}$ = AUC from zero time to 24 hours, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry, t_{max} = time at which the highest drug concentration occurs.

Additional Information: Quantification was conducted by a validated method described in Appendix 7 of Study No. 6700074. Lemborexant systemic exposure increased with increasing dose levels in a generally less than dose-proportional manner. C_{max} and $AUC_{(0\text{-}24)}$ on Day 269 were generally greater than those on Day 1, although some animals showed no increase. There were no sex related-differences.

2.6.5.5 薬物動態試験：分布

Test Article: lemborexant

CSF to Unbound Plasma Concentration Ratio in Rats **Study Number: 16-561** **Location in CTD: 4.2.2.2.1**

Strain/Gender/Number of Animals	Sprague Dawley/Male/4			
Feeding Condition	Fasted			
Vehicle / Formulation	200 mmol/L hydrochloric acid / Solution			
Method of Administration	Oral			
Dose	100 mg/kg			
Sample/Analyte / Assay	Plasma and CSF/Lemborexant, M4, M9, M10 / LC-MS/MS			
Time (h)	**CSF to Unbound Plasma Concentration Ratio**			
	Lemborexant	**M4**	**M9**	**M10**
1	0.442±0.101	0.166±0.040	0.385±0.066	0.219±0.033
2	0.533±0.163	0.160±0.023	0.442±0.104	0.228±0.063
4	0.513±0.114	0.143±0.039	0.429±0.127	0.212±0.063
8	0.558±0.158	0.147±0.023	0.431±0.081	0.216±0.029

The mean and SD of 4 individual values are presented. The CSF to unbound plasma concentration ratio was calculated from plasma and CSF concentrations and plasma protein binding of analytes (Lemborexant: 80.5%, M4: 54.9%, M9: 74.5%, and M10: 63.7%).

CSF = cerebrospinal fluid, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry.

Additional Information: This study also investigated the plasma pharmacokinetics (Section 2.6.5.3).

2.6.5.5 薬物動態試験：分布（続き）

Test Article: lemborexant

CSF to Unbound Plasma Concentration Ratio in Monkeys **Study Number: 16-562** **Location in CTD: 4.2.2.2.2**

Strain/Gender/Number of Animals	Cynomolgus/Male/4			
Feeding Condition	Fasted			
Vehicle / Formulation	200 mmol/L hydrochloric acid / Solution			
Method of Administration	Oral			
Dose	10 mg/kg			
Sample/Analyte / Assay	Plasma and CSF/Lemborexant, M4, M9, M10 / LC-MS/MS			
Time (h)	**CSF to Unbound Plasma Concentration Ratio**			
	Lemborexant	**M4**	**M9**	**M10**
1	0.142±0.040	0.124±0.017	0.197±0.079	0.262±0.045
2	0.493±0.087	0.419±0.168	0.824±0.263	0.730±0.264
4	0.771±0.153	0.509±0.108	0.752±0.280	0.632±0.125
8	1.08±0.15	0.465±0.052	0.570±0.173	0.947±0.073

The mean and SD of 4 individual values are presented. The CSF to unbound plasma concentration ratio was calculated from plasma and CSF concentrations and plasma protein binding of analytes (Lemborexant: 83.1%, M4: 63.9%, M9: 75.5%, and M10: 84.5%).

CSF = cerebrospinal fluid, CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry.

Additional Information: This study also investigated the plasma pharmacokinetics (Section 2.6.5.3).

2.6.5.5 薬物動態試験：分布（続き）

Test Article: [^{14}C]lemborexant

Rats **Study Number: 14-074** **Location in CTD: 4.2.2.3.1**

Strain/Gender/Number of Animals	Sprague Dawley/Male/3				
Feeding Condition	Fasted[a]				
Vehicle / Formulation	100 mmol/L hydrochloric acid / Solution				
Method of Administration / Dose	Oral, by using a polypropylene syringe with a gavage needle / 10 mg/kg				
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (K0110-030)				
Analyte/Assay	Radioactivity/Liquid scintillation counting				
Tissue/Organ	**Concentration of Radioactivity (ng eq./g or mL)**				
	1 h	**8 h**	**24 h**	**168 h**	**336 h**
Blood	970.1±52.1	331.8±19.4	41.8±7.9	15.4±0.1	BLQ
Plasma	696.9±137.6	317.9±18.7	36.9±5.7	9.9±1.3	BLQ
Blood cells	1456.6±37.5	311.1±19.4	45.8±6.6	27.2±6.0	BLQ
Cerebrum	222.8±87.2	49.1±3.8	BLQ	BLQ	—
Cerebellum	218.1±83.3	37.9±2.8	12.4±2.2	5.5±1.5	BLQ
Pituitary gland	1008.3±278.9	214.2±27.4	BLQ	BLQ	—
Medulla oblongata	268.2±99.5	42.8±4.0	17.1±2.7	4.7±2.4	BLQ
Spinal cord	335.2±129.3	47.2±5.1	16.6±2.6	5.6±0.4	BLQ
Eyeball	195.9±61.2	47.6±4.5	16.5±2.7	5.1±0.9	BLQ
Harderian gland	3139.5±1333.7	316.9±40.7	121.6±11.8	16.8±3.6	2.9±1.5
Mesenteric lymph node	1606.6±213.6	180.4±25.2	38.3±3.8	19.9±7.1	BLQ
Submaxillary gland	1097.6±325.7	216.7±42.8	35.8±6.3	5.8±1.2	BLQ
Thyroid gland	1318.4±296.4	443.3±65.5	74.2±37.2	BLQ	—
Trachea	996.5±447.9	151.2±9.2	34.5±5.1	17.7±0.6	BLQ
Heart	1098.8±334.5	156.4±14.0	30.9±6.4	7.0±1.6	2.0±0.5
Lung	1075.5±286.4	234.4±21.7	35.5±7.0	8.2±1.7	3.1±0.4
Thymus	561.2±239.7	89.7±8.4	18.6±3.6	4.4±0.6	BLQ
Fat	3640.9±1424.6	818.7±105.9	204.0±30.2	20.3±3.4	BLQ
Brown fat	6675.7±3707.4	352.3±67.3	85.5±7.3	11.1±1.3	5.8±0.5

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2.6.5.5 薬物動態試験：分布（続き）

Test Article: [^{14}C]lemborexant

Rats **Study Number: 14-074** **Location in CTD: 4.2.2.3.1**

Tissue/Organ	Concentration of Radioactivity (ng eq./g or mL)				
	1 h	8 h	24 h	168 h	336 h
Skin	1221.0±564.2	153.4±17.7	32.8±3.1	7.2±1.2	1.9±1.0
Skeletal muscle	588.5±149.4	79.3±10.0	22.2±4.0	8.6±3.5	3.2±1.8
Sciatic nerve	1643.2±880.7	176.1±22.2	41.5±5.6	BLQ	—
Bone marrow	759.9±198.9	139.0±10.0	27.3±5.6	BLQ	—
Testis	438.7±122.7	76.9±7.2	19.2±4.0	4.0±0.9	1.1±0.1
Seminal vesicle	616.1±161.8	115.4±28.8	35.3±12.5	4.5±1.2	1.2±0.6
Abdominal aorta	1504.5±389.9	197.0±42.1	41.9±21.0	BLQ	—
Inferior vena cava	1396.4±550.9	158.3±15.8	42.5±21.7	BLQ	—
Prostate gland	830.0±284.7	178.0±38.7	47.4±12.8	4.9±0.6	BLQ
Urinary bladder	757.3±153.8	592.9±188.2	54.3±8.4	11.4±6.2	BLQ
Spleen	784.7±201.0	133.7±16.1	32.3±6.5	10.1±1.4	4.7±1.3
Pancreas	1965.5±623.0	199.0±39.6	35.2±6.2	5.6±1.5	2.1±0.2
Adrenal gland	2590.2±804.1	316.4±22.3	64.0±12.7	21.5±1.1	BLQ
Kidney	2480.7±386.8	839.8±50.1	109.0±18.9	37.3±1.7	BLQ
Renal cortex	1648.6±450.5	713.1±76.4	100.2±17.9	22.5±5.4	BLQ
Renal medulla	908.1±271.2	746.9±13.5	62.6±8.5	14.8±7.4	BLQ
Liver	17,128.9±1998.8	4331.5±215.5	874.6±69.1	189.3±23.7	49.3±2.5
Stomach	32,733.1±175.0	237.5±50.1	39.0±7.5	5.1±1.0	1.4±0.3
Small intestine	12,145.5±673.3	1422.1±130.0	67.2±3.4	5.4±1.0	2.1±0.3
Cecum	1055.9±180.3	44,456.8±3493.0	277.7±50.2	7.1±1.6	2.9±0.4
Large intestine	1154.5±167.4	3037.8±895.3	138.1±31.2	4.5±0.9	2.4±0.1

Concentration of radioactivity was expressed as the equivalent of lemborexant (ng eq./g or mL). Values represent the mean ±SEM of 3 animals.

— = not collected, BLQ = below the limit of quantification, CTD = Common Technical Document, eq. = equivalent.

a: The fasting of the animals was started at 17:30 to 18:30 on the day before dosing (at least 16 hours before dosing) and terminated at 6 hours after administration. Water was given freely.

Additional Information: This study also investigated the blood level of radioactivity (Section 2.6.5.3), the excretion of radioactivity in urine and feces (Section 2.6.5.13), and the biliary excretion of radioactivity (Section 2.6.5.14).

2.6.5.5 薬物動態試験：分布（続き）

Test Article: [^{14}C]lemborexant

Rats (Pigmented) **Study Number: 14-188** **Location in CTD: 4.2.2.3.3**

Strain/Gender/Number of Animals	Brown Norway/Male/3							
Feeding Condition	Fasted[a]							
Vehicle / Formulation	100 mmol/L hydrochloric acid / Solution							
Method of Administration / Dose	Oral, by using a polypropylene syringe with a gavage needle / 10 mg/kg							
Radionuclide / Specific Activity (Lot No.)	[^{14}C] / [redacted] MBq/mg (K0110-030)							
Analyte/Assay	Radioactivity/Liquid scintillation counting							
Tissue/Organ	**Concentration of Radioactivity (ng eq./g or mL)**							
	1 h	**24 h**	**168 h**	**336 h**	**672 h**	**1344 h**	**2016 h**	**2688 h**
Blood	1134.9±158.4	56.6±2.3	17.7±0.4	7.8±4.1	BLQ	—	—	—
Plasma	712.6±133.4	52.2±1.9	BLQ	—	—	—	—	—
Blood cells	1460.8±182.3	52.4±2.5	27.3±1.7	15.6±0.6	BLQ	—	—	—
Cerebrum	219.3±51.2	BLQ	BLQ	—	—	—	—	—
Cerebellum	217.1±44.8	18.1±1.9	1.9±1.0	BLQ	—	—	—	—
Eyeball	475.3±99.9	43.6±1.5	10.8±0.3	5.8±0.8	BLQ	—	—	—
Heart	1087.5±257.1	37.8±1.4	6.4±0.2	2.1±0.0	BLQ	—	—	—
Lung	1019.2±220.9	45.4±1.6	7.5±0.2	3.3±0.1	1.9±0.2	1.5±0.1	2.3±0.4	BLQ
Skin	945.7±272.1	39.1±2.0	6.3±0.8	2.3±0.1	BLQ	—	—	—
Skeletal muscle	652.1±139.7	31.1±1.7	7.2±0.1	3.1±0.2	BLQ	—	—	—
Spleen	826.8±152.2	37.4±1.1	10.2±0.3	7.9±0.2	10.2±0.1	12.0±0.4	5.8±0.7	4.1±0.1
Kidney	2381.8±425.5	137.5±5.7	37.7±1.2	26.3±0.4	BLQ	—	—	—
Renal cortex	2150.0±374.6	161.0±5.1	25.5±3.5	15.9±0.8	BLQ	—	—	—
Renal medulla	1321.4±150.7	115.5±11.9	BLQ	—	—	—	—	—
Liver	17,001.7±3058.0	1203.7±81.3	213.3±7.2	72.6±4.2	BLQ	—	—	—

Concentration of radioactivity was expressed as the equivalent of lemborexant (ng eq./g or mL). Values represent the mean ±SEM of 3 animals.

— = not collected, BLQ = below the limit of quantification, CTD = Common Technical Document, eq. = equivalent.

a: The fasting of the animals was started at 17:30 to 18:00 on the day before dosing (at least 16 hours before dosing) and terminated at 6 hours after administration. Water was given freely.

Additional Information: This study also investigated the blood level of radioactivity (Section 2.6.5.3).

2.6.5.5 薬物動態試験：分布（続き）

Test Article: **[^{14}C]lemborexant**

Monkeys **Study Number: 14-075** **Location in CTD: 4.2.2.3.2**

Strain/Gender/Number of Animals		Cynomolgus/Male/3	
Feeding Condition		Fasted[a]	
Vehicle / Formulation		100 mmol/L hydrochloric acid / Solution	
Method of Administration / Dose		Oral, by using a polypropylene syringe with catheter / 3 mg/kg	
Radionuclide / Specific Activity (Lot No.)		[^{14}C] / [redacted] MBq/mg (K0110-030)	
Analyte/Assay		Radioactivity/Liquid scintillation counting	
Tissue/Organ		**Concentration of Radioactivity at 336 hours (ng eq./g or mL)**	**Distribution (% of the dose)**
Blood		BLQ	NC
Plasma		—	NA
Blood cells		BLQ	NA
Cerebral cortex		BLQ	NC
Cerebral medulla		BLQ	NC
Cerebellum		BLQ	NC
Pituitary gland		BLQ	NC
Medulla oblongata		0.4±0.2	0.00±0.00
Spinal cord		0.3±0.2	NA
Eyes	Cornea	BLQ	NC
	Aqueous humor	BLQ	NC
	Iris	45.4±4.3	0.00±0.00
	Ciliary body	13.6±1.7	0.00±0.00
	Lens	1.3±0.7	0.00±0.00
	Vitreous body	0.1±0.1	0.00±0.00
	Retina	0.7±0.5	0.00±0.00
	Choroid	15.9±2.3	0.00±0.00
	Sclera	BLQ	NC
	Optic nerve	BLQ	NA

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Test Article: [^{14}C]lemborexant

Monkeys **Study Number: 14-075** **Location in CTD: 4.2.2.3.2**

Tissue/Organ	Concentration of Radioactivity at 336 hours (ng eq./g or mL)	Distribution (% of the dose)
Mesenteric lymph node	6.3±1.1	NA
Submaxillary gland	1.4±0.1	0.00±0.00
Thyroid gland	3.2±0.2	0.00±0.00
Trachea	1.7±0.3	0.00±0.00
Heart	27.0±7.6	0.00±0.00
Lung	11.2±1.0	0.00±0.00
Gallbladder	62.1±18.7	0.00±0.00
Thymus	1.9±0.3	0.00±0.00
Fat	18.8±1.9	0.05±0.01
Brown fat	8.0±1.2	NA
Skin	6.8±0.9	0.02±0.00
Skeletal muscle	1.2±0.0	0.02±0.00
Sciatic nerve	2.0±0.1	NA
Bone marrow	5.8±0.5	NA
Testis	1.5±0.1	0.00±0.00
Abdominal aorta	BLQ	NA
Inferior vena cava	4.5±2.7	NA
Prostate gland	1.6±0.9	0.00±0.00
Urinary bladder	BLQ	NC
Spleen	BLQ	NC
Pancreas	8.3±3.3	0.00±0.00
Adrenal gland	4.3±0.3	0.00±0.00
Kidney	18.7±1.2	0.00±0.00
Renal cortex	18.3±2.2	NA
Renal medulla	11.3±0.7	NA
Liver	245.3±10.2	0.14±0.01

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Test Article: **[^{14}C]lemborexant**

Monkeys **Study Number: 14-075** **Location in CTD: 4.2.2.3.2**

Tissue/Organ	**Concentration of Radioactivity at 336 hours (ng eq./g or mL)**	**Distribution (% of the dose)**
Stomach	1.9±1.0	0.00±0.00
Small intestine	11.0±2.2	0.00±0.00
Cecum	17.5±1.5	0.00±0.00
Large intestine	9.3±3.7	0.00±0.00
Urine in urinary bladder	11.1±1.6	0.00±0.00
Bile in gallbladder	796.9±83.6	0.01±0.00

Concentration of radioactivity was expressed as the equivalent of lemborexant (ng eq./g or mL). Values represent the mean ±SEM of 3 animals.

— = not collected, BLQ = below the limit of quantification, CTD = Common Technical Document, eq. = equivalent, NA = not applicable, NC = not calculated.

a: The fasting of the animals was started from 18:00 on the day before the dosing (at least 16 hours before dosing) to 6 hours after the dosing. Water was given freely.

Additional Information: This study also investigated the blood level of radioactivity (Section 2.6.5.3) and the excretion of radioactivity in urine and feces (Section 2.6.5.13).

2.6.5.6 薬物動態試験：タンパク結合

Test Article: lemborexant

Plasma Protein Binding of Lemborexant **Study Number: 12-304** **Location in CTD: 5.3.2.1.1**

Study System	in vitro			
Test System	Plasma			
Method	Equilibrium dialysis against phosphate-buffered saline (pH 7.4) for 17 hours at 37 °C			
Assay / Analyte	LC-MS/MS / Lemborexant			
Concentration	100, 300, and 1000 ng/mL			
Species (plasma)	**Compound**	**Protein Binding (%)**		
		Concentration (ng/mL)		
		100	**300**	**1000**
Mouse	Lemborexant	87.1±0.1	86.8±0.9	86.7±0.7
Rat		82.4±1.2	80.6±1.2	78.4±0.7
Monkey		83.4±0.2	83.4±0.3	82.4±0.3
Human		88.7±0.1	88.4±0.4	87.4±0.8

Values represent the mean ±SEM of 3 determinations. Pooled blank plasma was used in mice, and individual blank plasma was used in rats, monkeys, and humans. In all species, gender was male.

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry.

Additional Information: No apparent concentration dependency in the plasma protein binding of lemborexant was observed in all the species examined.

2.6.5.6 薬物動態試験：タンパク結合（続き）

Test Article: M4, M9, M10

Plasma Protein Binding of Lemborexant Metabolites **Study Number: 16-559** **Location in CTD: 5.3.2.1.2**

Study System	in vitro			
Test System	Plasma			
Method	Equilibrium dialysis against phosphate-buffered saline (pH 7.4) for 12 hours at 37 °C			
Assay / Analyte	LC-MS/MS / Lemborexant metabolites, M4, M9, and M10			
Concentration	100, 300, and 1000 ng/mL			
Species (plasma)	**Compound**	**Protein Binding (%)**		
		Concentration (ng/mL)		
		100	**300**	**1000**
Mouse	M4	66.1±1.3	66.3±1.1	64.5±0.7
Rat		55.7±3.0	53.1±1.5	55.9±2.8
Monkey		63.1±2.5	63.5±0.9	65.0±1.8
Human		74.3±0.0	74.4±0.8	74.4±0.5
Mouse	M9	74.4±0.6	73.4±0.6	71.0±0.8
Rat		74.5±1.3	74.3±0.9	74.6±1.0
Monkey		77.2±0.7	74.2±0.6	75.1±0.7
Human		85.7±0.6	86.2±0.9	85.3±0.5

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Test Article: M4, M9, M10

Plasma Protein Binding of Lemborexant Metabolites **Study Number: 16-559** **Location in CTD: 5.3.2.1.2**

Species (plasma)	Compound	Protein Binding (%)		
		Concentration (ng/mL)		
		100	300	1000
Mouse	M10	65.2±0.8	68.4±1.0	67.5±1.4
Rat		61.3±1.5	65.3±0.8	64.5±2.2
Monkey		84.4±1.7	84.7±1.2	84.3±1.3
Human		91.5±0.2	91.9±0.6	92.0±0.3

Values represent the mean ±SEM of 3 determinations. Pooled blank plasma was used in mice, and individual blank plasma was used in rats, monkeys, and humans. In all species, gender was male.

CTD = Common Technical Document, LC-MS/MS = liquid chromatography with tandem mass spectrometry.

Additional Information: Species differences in plasma protein binding of M4, M9, and M10 were observed and all metabolites tested showed the highest protein binding in humans. No apparent concentration dependency in plasma protein binding of M4, M9, and M10 was observed in all species tested.

2.6.5.6 薬物動態試験：タンパク結合（続き）

Test Article: lemborexant

Binding to Human Serum Protein **Study Number: DMPKT2017-003** **Location in CTD: 5.3.2.1.3**

Study System	in vitro		
Test System	Human protein in blood		
Method	Equilibrium dialysis against phosphate-buffered saline (pH 7.4) for 24 hours at 37 °C		
Assay / Analyte	LC-MS/MS / Lemborexant		
Concentration	100, 300, and 1000 ng/mL		
Plasma Protein (concentration)	**Protein Binding (%)**		
	100 ng/mL	**300 ng/mL**	**1000 ng/mL**
Human serum albumin (40 mg/mL)	73.2±0.3	73.5±0.3	74.0±0.5
α1-Acid glycoprotein (1.0 mg/mL)	13.1±0.6	10.3±1.1	9.3±0.4
Human γ-globulin (15 mg/mL)	9.4±1.6	7.4±2.9	6.0±1.7
Low-density lipoprotein (3.5 mg/mL)	78.6±0.3	78.9±0.1	77.9±0.2
High-density lipoprotein (4.0 mg/mL)	70.6±0.3	70.3±0.1	70.6±0.1

Values represent the mean ±SEM of 3 determinations.

α1-AGP = α1-acid glycoprotein, CTD = Common Technical Document, HDL = high-density lipoprotein, HG = human γ-globulin, HSA = human serum albumin, LC-MS/MS = liquid chromatography with tandem mass spectrometry, LDL = low-density lipoprotein.

Additional Information: Lemborexant primarily binds to HSA, LDL, and HDL in human plasma, and that the contribution of α1-AGP and HG to the plasma protein binding of lemborexant in humans is minor.